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Inflammation in CNS neurodegenerative diseases

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Summary

Neurodegenerative diseases, the leading cause of morbidity and disability, are gaining increased attention as they impose a considerable socioeconomic impact, due in part to the ageing community. Neuronal damage is a pathological hallmark of Alzheimer's and Parkinson's diseases, amyotrophic lateral sclerosis, Huntington's disease, spinocerebellar ataxia and multiple sclerosis, although such damage is also observed following neurotropic viral infections, stroke, genetic white matter diseases and paraneoplastic disorders. Despite the different aetiologies, for example, infections, genetic mutations, trauma and protein aggregations, neuronal damage is frequently associated with chronic activation of an innate immune response in the CNS. The growing awareness that the immune system is inextricably involved in shaping the brain during development as well as mediating damage, but also regeneration and repair, has stimulated therapeutic approaches to modulate the immune system in neurodegenerative diseases. Here, we review the current understanding of how astrocytes and microglia, as well as neurons and oligodendrocytes, shape the neuroimmune response during development, and how aberrant responses that arise due to genetic or environmental triggers may predispose the CNS to neurodegenerative diseases. We discuss the known interactions between the peripheral immune system and the brain, and review the current concepts on how immune cells enter and leave the CNS. A better understanding of neuroimmune interactions during development and disease will be key to further manipulating these responses and the development of effective therapies to improve quality of life, and reduce the impact of neuroinflammatory and degenerative diseases.

Keywords: immune response; inflammation; microbiome; neuroprotection; repair.

Introduction

The prevalence of neurodegenerative diseases highly depends on the country surveyed, yet the most prevalent disease globally is dementia, with an estimated incidence of 9·33% worldwide[1] (Table 1). The increase in the incidence of dementia, as with many neurodegenerative diseases, is in part due to the ageing population,[2] as an

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; AQP4, aquaporin 4; Aβ, amyloid-beta; BBB, blood–brain barrier; BSCB, blood–spinal cord barrier; CNS, central nervous system; COX-2, cyclooxygenase-2; CP, choroid plexus; CVD, cerebrovascular diseases; EV, extracellular vesicles; EVD, Ebola virus disease; FTD, frontotemporal dementia; GDNF, glial cell-derived neurotrophic factor; HD, Huntington's disease; HIV, human immunodeficiency virus; HSPs, heat-shock proteins; IFN-γ, interferon gamma; MHC, major histocompatibility complex; MRI, magnetic resonance imaging; MS, multiple sclerosis; NF, neurofilament light; NK, natural killer; PD, Parkinson's disease; PET, positron emission tomography; PNND, paraneoplastic neurological disorders; PrP, prion protein; ROS, reactive oxygen species; SMA, spinal muscular atrophy; SPECT, single-photon emission computed tomography; TBI, traumatic brain injury; TDP-43, TAR DNA-binding protein 43 kD; TLRT, oll-like receptor; TNF-α, tumour necrosis factor alpha; TREM2, triggering receptor expressed on myeloid cells 2; ZIKV, Zika virus; ZO-1, zonula occludens-1

ageing brain, or one following peripheral infections or other insults is 'primed' to render the central nervous system (CNS) more susceptible to damage.[3] Priming of innate immune responses in the CNS may thus explain the higher prevalence of epilepsy in developing countries[4] where CNS infections[5] with neurotropic viruses are more frequent. The neurotropic virus Zika is a good example of how such viral infections not only contribute to neurodegenerative diseases in the elderly, but also have a major impact during development.

Despite different aetiologies (Table 1), a common feature of neurodegenerative diseases is chronic activation of innate immune cells within the CNS, and in other diseases such as multiple sclerosis (MS), the influx of peripheral immune cells across the blood–brain barrier (BBB). Old notions on how cells traffic into the CNS, despite an apparently immune-privileged environment, have been challenged recently by the identification of lymphatic drainage, as well as by detailed studies on immune cell trafficking in the choroid plexus (CP).

Here, we review the recent advances in our understanding of how immune responses in the CNS contribute to susceptibility to neurodegenerative diseases, how immune responses change with ageing, and how therapies can be designed to augment reparative processes in the CNS.

Immune privilege and CNS barriers

The concept of immune privilege originated from Sir Peter Medawar's studies in the mid-20th century showing that tissue grafts in the CNS were not rejected. It also takes into account the presence of the BBB, revealed by Paul Ehrlich's studies in the late 1800s showing that solutes and molecules were excluded from the brain. However, it is now clear that entry of compounds into the CNS occurs via capillary venules, while cell migration occurs at the post-capillary venules and is controlled by adhesion molecules, cytokines and chemokines.[35] Anatomically, the CNS is separated by three barriers: the BBB/blood–spinal cord barrier (BSCB); the blood–cerebrospinal fluid barrier at the CP (Fig. 1); and the arachnoid barrier. Differences in the structure of the BBB and BSCB, as well as differences in the cranial and spinal meninges, in white and grey matter, and other regional differences may explain the differential susceptibility of anatomical regions to neuroinflammmatory events. For example, the BSCB has reduced levels of zonula occludens-1 (ZO-1), occludin, VE cadherin and P-gp, and fewer pericytes than the BBB,[36] indicating that the spinal cord may well be more susceptible to inflammatory insults than the brain. The presence of barriers originally explained why CNS antigens in the brain were ignored by the peripheral immune response. However, this dogma has been challenged recently by the identification of the glymphatic system[37] and rediscovery of lymphatic vessels in the dura mater[38,39] that are crucial to clear waste products such as amyloid-beta (Aβ) peptides and tissue debris that accumulate during disease. Dysfunction of these barriers is well known to occur in neuroinflammatory disorders, including MS, Parkinson's disease (PD), Alzheimer's disease (AD), stroke, epilepsy and traumatic brain injury (TBI),[40] and is associated with activated endothelial cells that display an altered phenotype and a decrease in tight junction proteins. These changes that are also observed during ageing[41] may explain the increase in susceptibility to neuroinflammation and neurodegenerative disorders in the elderly. As well as playing a protective role in neuromyelitis optica (NMO), the BBB is also a target of immune responses where pathogenic autoantibodies to aquaporin 4 (AQP4) damage astrocytes that otherwise maintain BBB.

Innate immunity

Innate immunity is the first line of defense in infection, but also plays a key role in tissue repair, clearance of apoptotic cells and cellular debris, as well as in response to tumours. While the key innate immune cells in the CNS are microglia and astrocytes, macrophages, natural killer (NK) cells and mast cells as well as oligodendrocytes and neurons all contribute to innate immune responses in the CNS. Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) include misfolded and aggregated proteins as in, for example, AD, amyotrophic lateral sclerosis (ALS), Huntington's disease (HD) and PD.[42] Cellular receptors that recognize PAMPS and DAMPs, such as endogenous molecules, for example, heat-shock proteins (HSPs), viral and bacterial antigens, and oxidized lipids, include the Toll-like receptors (TLR), C-type lectins and oxidized lipoprotein detectors and nuclear oligomerization domain-like receptors (NLRs) that play a key role in the inflammasome. That innate receptors, for example, triggering receptor expressed on myeloid cells 2 (TREM2), are key to aiding clearance of dying cells, myelin debris and aggregated proteins may explain the association of a rare variant in TREM2 with AD, ALS and PD.[42]

Microglia, the principal resident innate immune cells of the CNS, have diverse functions. During development they shape neural circuits by pruning synapses as well as regulating cell death and elimination of waste products during inflammation or CNS damage. Differential activation of microglia is often classified as being either classical (M1) or alternative (M2), based on chemokine and cytokine expression *in vivo*.[43] Switching between these polarizations is vital for remyelination and is affected by ageing, as shown by the use of parabiosis in mice.[44] Microglia secrete pro-inflammatory as well as anti-inflammatory factors, which can either be beneficial or detrimental in neurodegenerative diseases,[45] for example

Table 1. Aetiology, immune involvement and incidence of neuroinflammatory diseases

Disease	(Proposed) Aetiology	Innate immune response involvement	Adaptive immune response involvement	Incidence % or number/ 100 000	Predicted change in prevalence	References
MS	Autoimmune viral	Microglial and macrophage activation, ↑ROS, complement, ↑innate receptors, ↑cytokines, ↑chemokines	↑HSPs, ↑neurotrophins, antibodies and T-cells to CNS antigens. Effective therapies target B-cells	9·64	↑2·4% per year	6,7
AD, other dementias	AD – misfolded and aggregated tau and APP	Activated and dystrophic microglia, ↑TNF-α, ↑IFN-γ, ↑chemokines, ↑complement, ↑TLRs	↑antibody and T-cell response	9·33%	↑3·3% per year (triple by 2050)	6, 1, 2
PD	Selective loss of dopaminergic neurons in substantia nigra due to α-syn- intraneuronal inclusions	↑TLRs, ↑CD14, activated NK cells, microglial activation, ↑IL-1β, ↑IL-6, ↑TNF-α	↑T-cells, ↑antibody response	100–200	Double in 25 years	6, 8, 9
HD	Expansion of CAG (Q) in huntingtin gene induces aberrant toxic protein	↑microglial proliferation, ↑complement,	Not reported	0·02–9·71	↑15–20% per decade	6,10
SMA	Genetic defect in the SMN1 gene	↑IL-6, ↑IL-1β	Not reported	1–2	Not reported	6, 11
ALS (MND)	Aberrant aggregated proteins due to mutations SOD1, TDP; C9orf72 or FUS genes	↑complement, ↑CD14, ↑macrophages, ↑IL-6, ↑TNF-α	↑$CD4^+$, ↑$CD8^+$ T-cells	1·9	↑69% in 25 years	6, 12, 13
Prion diseases	Infectious forms of misfolded aggregated forms of prion protein	↑microglial activation, ↑IL-1β, ↑IL-6, ↑complement, ↑ROS, mast cells expressing PrP	B-cells aid transport of PrP	Variable	Not reported	6
Stroke	Ischaemia (thrombosis, embolism, or systemic hypoperfusion) or haemorrhage (intra-cerebral or subarachnoid)	↑lymphopenia, ↑NK cells, ↑IL-10	↑Th2 responses	115	↑44% in 20 years	14, 15, 26
TBI	Open and head injury, deceleration injuries, chemical/toxic, hypoxia, tumours,	↑pro-inflammatory cytokines, ↑TLRs	↑T-cells, ↑B-cells	295	Not reported	6, 16
HIV/AIDS	HIV encephalopathy, toxoplasmosis, PML	↓IL-27, ↓IFN-γ, ↓CD4 cells, ↑IL-4	↓T-cells, immunosenescence	0·8%	Depending on country	17, 27
Meningitis	Bacterial and viral infections	↑IL-6, ↑TNF-α, ↑NK cells, ↑microglial activation	↑T-cells, ↑B-cells	0·2–1000	Outbreak dependent	18, 29
Ageing	Natural event	↑pro-inflammatory cytokines, ↓NK cell function	↓T-cells	n/a	n/a	28
Epilepsy	Unprovoked seizures, febrile events, autoantibodies,	↑pro-inflammatory cytokines, ↑chemokines, ↑TLRs, ↑complement	↑autoantibodies, T- and B-cell activation	45–81·7	↑	6, 4, 5
Autism	Genetic and environmental	↑pro-inflammatory cytokines	↓T-cells	425–760	Variable	19, 20, 30

Table 1. *(Continued)*

Disease	(Proposed) Aetiology	Innate immune response involvement	Adaptive immune response involvement	Incidence % or number/ 100 000	Predicted change in prevalence	References
Depression	Multifactorial e.g. genetics, hormonal	Microglial activation, ↑ cytokines, ↑chemokines	↑ T-reg cells	3%	↑	21, 22, 31
Schizophrenia	Multifactorial	Microglial activation, ↑ROS, ↑pro-inflammatory cytokines, ↑chemokines, ↑TLRs, ↓NK cells	Not reported	18·5	Not reported	23, 32, 33
Bipolar disorder	Genetic and environmental risk factors	Microglial activation, ↑pro-inflammatory cytokines, ↑complement, ↑TNF-α	↑T-cell activation	2·4% lifetime prevalence	Debated	24, 25, 34

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APP, amyloid-β precursor protein; FUS, fused in sarcoma; HD, Huntington's disease; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; MS, multiple sclerosis; PD, Parkinson's disease; PML, progressive multifocal leucoencephalopathies; SMA, spinal muscular atrophy; SOD1, superoxide dismutase 1; SMN, survival of motor neuron protein; TBI, traumatic brain injury, TDP-43, TAR DNA-binding protein 43 kDa.

microglia depletion in a mouse model of AD reduced neuronal loss without affecting Aβ pathology.[46] Microglia-derived factors such as brain-derived neurotrophic factor are important for learning and memory processes, processes that can be affected by maternal inflammation leading to disrupted behaviour and learning in later life.[47] Microglia appear to have different transcriptomic profiles dependent on the region of the brain, ageing,[48] neuropathological state[45] and the microbiome.[49]

Monocytes are the blood-borne precursors to macrophages and dendritic cells, and play a key role in innate immunity. While microglia, in contrast to other tissue-resident macrophages, arise from yolk sac primitive macrophages, their distinct roles in CNS disorders are frequently hard to distinguish. The development of the CCR2-red fluorescent protein knock-in mouse has allowed researchers to better differentiate the infiltrating monocytes/macrophages and resident microglia in experimental diseases.[50] In addition, the novel markers TMEM119 and P2Y12 have also helped differentiate microglia and macrophages,[51] allowing the relative contribution of these cells in neuroinflammatory diseases to be examined.

Similar to the M1/M2 polarization of macrophages and microglia, subpopulations of astrocytes have been reported that produce pro-inflammmatory mediators (A1) and immunoregulatory mediators (A2). The A1 astrocytes that secrete Il-1a, tumour necrosis factor alpha (TNFα) and C1q are considered to be neuroinflammatory, and damage neurons and oligodendrocytes *in vitro* as well as inducing apoptosis, suppressing T helper cell activation, proliferation and function of activated T-cells. In contrast, A2 astrocytes are neuroprotective, promoting neuronal growth, survival and synaptic repair.[52] Astrocytes respond to a plethora of insults and are frequently observed as hypertrophic in many neurodegenerative diseases, including stroke, TBI, MS, ALS and viral infections and other inflammatory conditions.[52] A1 reactive astrocytes have been suggested as having toxic effects in ALS, AD, MS, PD, HD, schizophrenia and ageing,[52,53] whilst synapse-promoting A2 astrocytes may be responsible for unwanted synapses in epilepsy and neuropathic pain.[54] As well as the classical innate immune cells, i.e. microglia and astrocytes, oligodendrocytes also contribute to innate immune reactions, expressing receptors and producing immunomodulatory cytokines and chemokines. During CNS insults and disease, oligodendrocytes can aid protective and regenerative processes, but can also contribute to neurodegeneration through poor production or repair of myelin. Cross-talk between oligodendrocytes and microglia is a key area of interest in many CNS diseases.[55] NK cells have long been considered as lymphocytes that kill tumour cells and virally infected cells. However, recent studies have identified regulatory roles in T-cell responses and homeostasis. Dysfunction of these regulatory roles

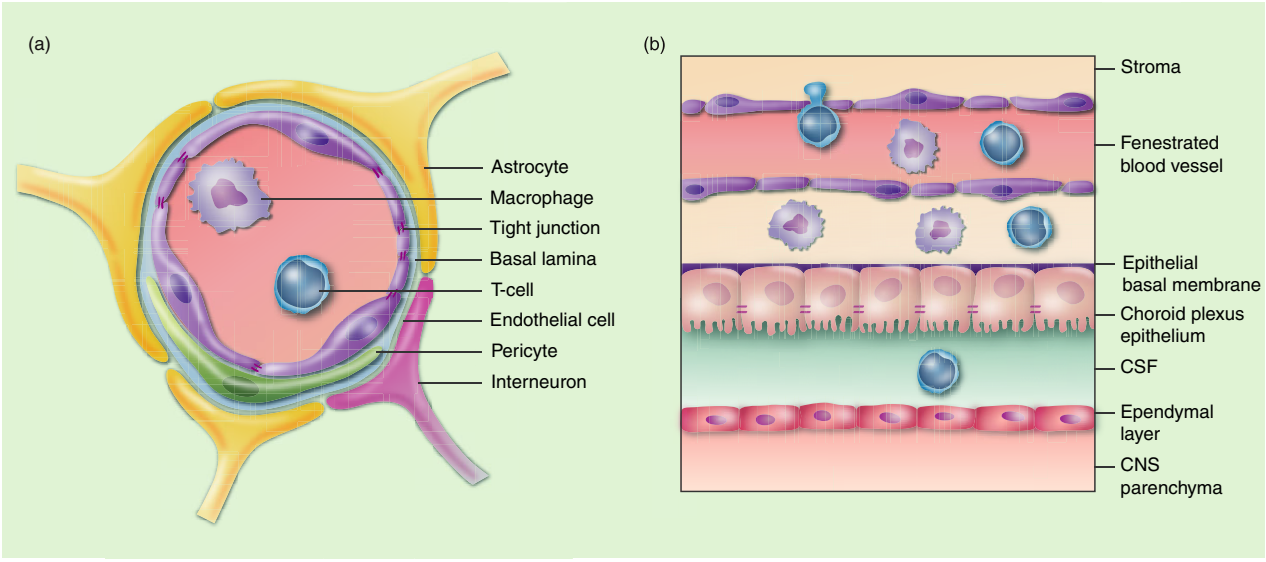

Figure 1. Blood–central nervous system (CNS) barriers. The blood–brain barrier (BBB) (a) and blood–spinal cord barrier (BSCB) (that resembles the BBB, see text for details) limit potential immune cells (shown in the lumen of the blood vessel), antibodies and soluble factors entering the CNS in health. Likewise, while the choroid plexus (CP) also limits cell migration, evidence suggests that regulatory T-cells enter the brain via the CP (b) during health in order to ensure surveillance of the CNS (see text for details). CSF, cerebrospinal fluid.

has been linked to MS,[56] and reduced levels of NK cells have been found in depression.[57] Mast cells mediate BBB permeability and recruitment of immune cells into the brain, sustaining CNS inflammation in a potentially detrimental manner.[58] Recent studies show that mast cells interact with the gut microbiota and gut permeability, and may therefore influence many diseases in which the gut microbiota is of importance, including MS, AD, ALS, PD and epilepsy.[59]

The complement system is an ancient part of the immune system, which protects from microbes, removes debris and promotes cell survival. Recent studies have highlighted further roles of the complement system, including control of cellular reprogramming and intracellular metabolic programming.[60] These newly discovered functions are still under investigation, and their meaning could have important relevance for therapeutic targeting as the complement system has been implicated in many diseases, including AD, ALS, MS, PD, epilepsy, TBI, schizophrenia and depression, predominantly through driving inflammation.[61] It is now emerging that the complement system may form a link between innate and adaptive immunity, aiding in stimulation and regulation of lymphocytes, and antigen presentation.[62]

The classical image of innate immunity being strictly non-specific has been confounded in recent times, with emerging evidence of innate immunity having some memory capacity, mostly through epigenetic changes. Monocytes, macrophages and NK cells have all been shown to have enhanced responses to previously-encountered insults, although less specific than adaptive immune responses.[63]

Adaptive immunity

The role of adaptive immunity in neurodegenerative disorders is supported by alterations in T- and B-cell subsets and (auto)antibody levels in the blood, cerebrospinal fluid (CSF) and brain tissues during disease (Fig. 2). Whether the cell subsets have a detrimental role (i.e. Th1 or Th17), or anti-inflammatory role [i.e. Th 2 or regulatory cells (Tregs)] is based, for example, on cytokines and chemokines profiles. The role of the adaptive immune responses in neurological diseases is best illustrated by the spectrum of autoimmune encephalopathy syndromes, including the paraneoplastic neurological disorders (PNND).[64,65] In many of these disorders the use of IVIG or removal of the tumour expressing the aberrant antigen in PNND is frequently sufficient to treat these disorders. Traditionally, MS has been characterized by the invasion of the CNS by adaptive immune cells, i.e. T and B lymphocytes; however, the role of the adaptive immunity in PD and ALS is gradually gaining interest, although in AD the inflammation is primarily by CNS-resident microglia. For example, in early PD, increased numbers of Th17 cells are observed in the blood, some of which recognize α-synuclein,[66] although whether these T-cells are pathogenic is unclear. T- and B-cells are also present in the CNS during X-ALD, and may represent a secondary phenomenon as immunosuppressive therapies have little

impact on the course of the disease. In mouse models of ALS, lower numbers of Tregs are concomitant with motor neuron death and shorter survival times, while transfer of Tregs suppresses neuroinflammation and prolongs survival. In line with these findings, Tregs have been reported to be dysfunctional in people with ALS,[67] although the relevance for the disease progression has not been examined. In an experimental model of AD T-cells aid clearance of plaques in transgenic mice yet also drive the pathology and cognitive impairments that can be rectified using anti-CD3 or IL-2 treatment.[68,69] That T-cells are more likely to be beneficial in AD is supported by studies showing that transplantation of splenocytes from young mice improved spatial learning and memory in amyloid precursor protein (APP)swe/PSENldE9 transgenic mice.[70] Whether aged T-cells in AD are pathogenic is unknown; however, such protection in early life may be due to haematopoietic stem cell proliferation known to reduce with age,[71] leading to a decrease in naïve and memory B-cells, impaired antibody levels, number and function[72] of T-cells characterized by an inverted $CD4^+$/$CD8^+$ ratio, and an accumulation of $CD8^+/CD28^-$ cells.[73]

That the adaptive immune response plays a major role in early MS is evidenced by the effectivity of anti-inflammatory therapies that modify the natural evolution of disease. Although widely-considered to be a T-cell-mediated disease, CD20 therapy is surprisingly effective, indicating a key role of B-cells in the disease. This is further supported by recent data indicating memory B-cells are major targets for effective immunotherapy in relapsing–remitting MS.[74] However, approaches targeting the adaptive immune response are less effective when administered to patients in the progressive phase of the disease, indicating a less important role for B-cells in disease progression.

In addition to the cellular involvement, the presence of immunoglobulins, i.e. oligoclonal IgG in the CSF, is a diagnostic marker in MS; however, it is still unclear whether these antibodies are pathogenic, or merely arise due to aberrant intrathecal B-cells activated by Epstein–Barr virus infection. This issue remains controversial and deserves further study. In contrast to the as yet unknown role of antibodies in MS, the closely related disorder NMO, once classified within the MS spectrum, is now considered a separate entity as the identification of the target antigen of the antibody was identified as the water channel AQP4. That antibodies to AQP4 are pathogenic has been demonstrated in animal models and also *in vitro*, resulting in astrocyte damage.[75]

Microbiome

Emerging evidence indicates that the microbiome influences CNS function and that disturbances in the microbiota–gut–brain axis may play a key role in susceptibility to, as well as augmenting, neuroinflammatory disorders (Fig. 3). Systemic infections contribute to neurodegenerative disorders[76] by 'priming' innate immune cells in the CNS, implying that priming may also occur following release of microbiome bacteria, viruses, fungi and protozoa, and their toxins and metabolic products. The composition of the gut microbiome is largely dictated by early-life occurrences, such as caesarean section,[77] breastfeeding and the early use of antibiotics. During infancy to adulthood, the microbiome is relatively stable, although changes may occur in later life when neurodegenerative diseases arise.[78] That recent studies have linked functional alterations in the gut microbiota to several neurodegenerative diseases, for example, ALS, AD, MS, PD, autism, bipolar disorder, depression and schizophrenia,[79–81] suggests that such alterations may contribute to disease. In AD and PD, exposure to gut bacterial infections is associated with disease,[82,83] and in AD and MS, fewer anti-inflammatory gut bacteria and an increase in pro-inflammatory gut bacteria are associated with disease.[79] Furthermore, the gut microbiome from people with MS were shown to induce experimental neurological disease in mice,[84] supporting the notion that some components of the microbiome activate a pathogenic inflammatory response. Conversely, some gut bacteria regulate immune responses, raising the possibility that probiotic biotherapies or faecal microbiota transplants may be therapeutic for a range of inflammatory diseases, including neurodegenerative diseases.[85]

Environmental triggers and lifestyle risk factors

Several neurodegenerative diseases are clearly genetic, for example, spinal muscular atrophy (SMA), genetic white matter disorders, HD, spinocerebellar ataxia and familial forms of ALS. However, the age of onset, progression and severity of disease are often influenced by environmental factors and lifestyle risk factors, such as smoking.[86] For example, family members of people with ALS share the same 'causal' genetic mutation, yet may develop disease onset at considerably different ages, some with, and some without, cognitive impairment.[87] A recent study showed an increased risk for ALS in areas with higher concentrations of airborne pollutants,[88] and many other environmental factors have also been implicated. Such variation is also seen in MS, of which where the incidence is influenced by latitude and vitamin D.[89] Identification of environmental risk factors is highly reliant on large epidemiological studies, which usually report only weak associations between risk factors and disease. However, many environmental and lifestyle factors increase the risk of several neurodegenerative and neuroinflammatory diseases (Table 2).

An emerging threat that is spreading rapidly in nearly all countries on the American continents is the flavivirus

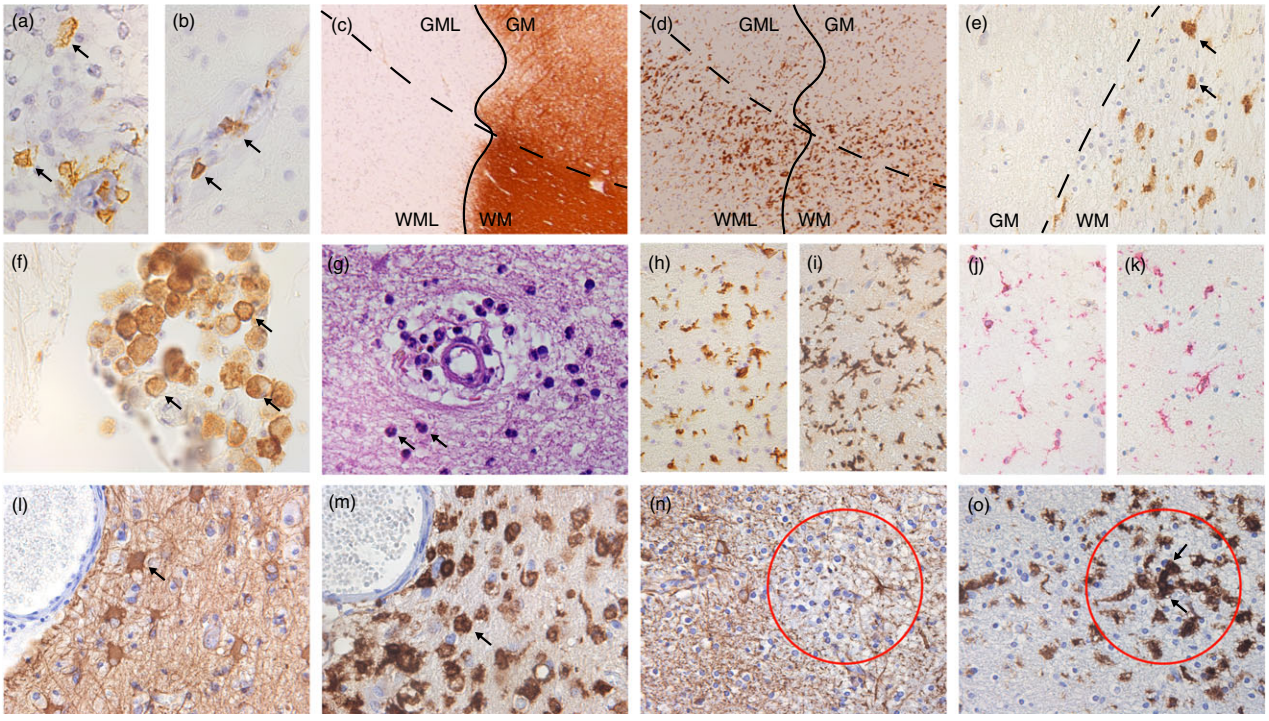

Figure 2. Immune responses in human and experimental inflammatory neurodegenerative disorders. B-cells (arrows) are observed in white (a) and grey matter lesions (b) in multiple sclerosis (MS). (c) and (d) depict an MS leucocortical lesion. The white matter (WML) is associated with HLA^+ microglia (d, WML) in contrast to the lack of HLA^+ microglia in the grey matter (d, GML). A similar pattern of HLA^+ cells is seen in the white and grey matter in an X-ALD case (e) and where peripheral macrophages infiltrate the white matter (f). Granulocytes (arrow) in suspected vasculitis cases (g). Ageing influences the activity of microglia in a mouse model of MS: microglia in the central nervous system (CNS) of young mice (h; Iba1 staining) are less active than in aged mice (i). In MS cases microglia in normal appearing white matter express P2Y12 (j) and TMEM119 (k). In progressive multifocal leucoencephalopathy astrocytes (l, arrow) and activated microglia/macrophages (m, arrow) are highly reactive in an area of demyelination. The paucity of astrocytic glial fibrillary acidic protein expression (red circle, n) is associated with an area of microglial activation (red circle, o) in acute haemorrhagic leucoencephalitis.

Zika (ZIKV).[100] The tropism of ZIKV has been reported to be directed to neurons and neural stem cells, increasing its risk in CNS disease development. Despite the asymptomatic nature of ZIKV infection in adults, neurological complications have been reported in children, including Guillain–Barré syndrome, myelitis, seizures and meningoencephalitis.[100] Another recent, yet more deadly, virus is Ebola (EVD), with a mortality rate ranging up to 90%.[101] The recent outbreak in 2014 has given insight into its pathological mechanisms as it can cross the BBB and affect the CNS during infection. Subsequently, EVD has been reported to cause neurological symptoms such as seizures and delirium, while on a neuropathological level glial nodules, (chorio)meningoencephalitis, perivascular cuffing and cerebral haemorrhages are found.[101]

Ageing

Ageing, a major risk factor in neurodegenerative diseases, has a predominantly negative effect on both innate and adaptive immune responses, reducing the efficacy of vaccinations, and increasing susceptibility to infectious, chronic, autoimmune and neurodegenerative diseases.[72] Ageing has been associated with a low-grade sterile inflammatory status of the immune system, frequently termed *inflammaging*,[102] in which pro-inflammatory cytokines (e.g. IL-6, TNF, IL-1β) are key players in unhealthy ageing. Inflammaging might be the most important aetiological factor in age-related neurodegenerative diseases, as 'neuro-inflammaging' is associated with significantly decreased numbers of neurons, neuronal arborization, spines and cortical volume.[103] With ageing, both macrophages and microglia display impaired and prolonged activation to insults, reduced motility and impaired phagocytosis.[104] This over-activation induces reactive oxygen species (ROS) production and attracts peripheral leucocytes, which affects the metabolic and trophic support glial cells provide their environment.[105] Impaired phagocytosis results in increased toxic protein accumulation, which is associated with progressive pathology of Aβ in AD and α-synuclein in PD.[106] Furthermore, the self-renewing capacity of glial cells drives telomere shortening, which was found to contribute towards AD pathology.[107] While not yet fully investigated

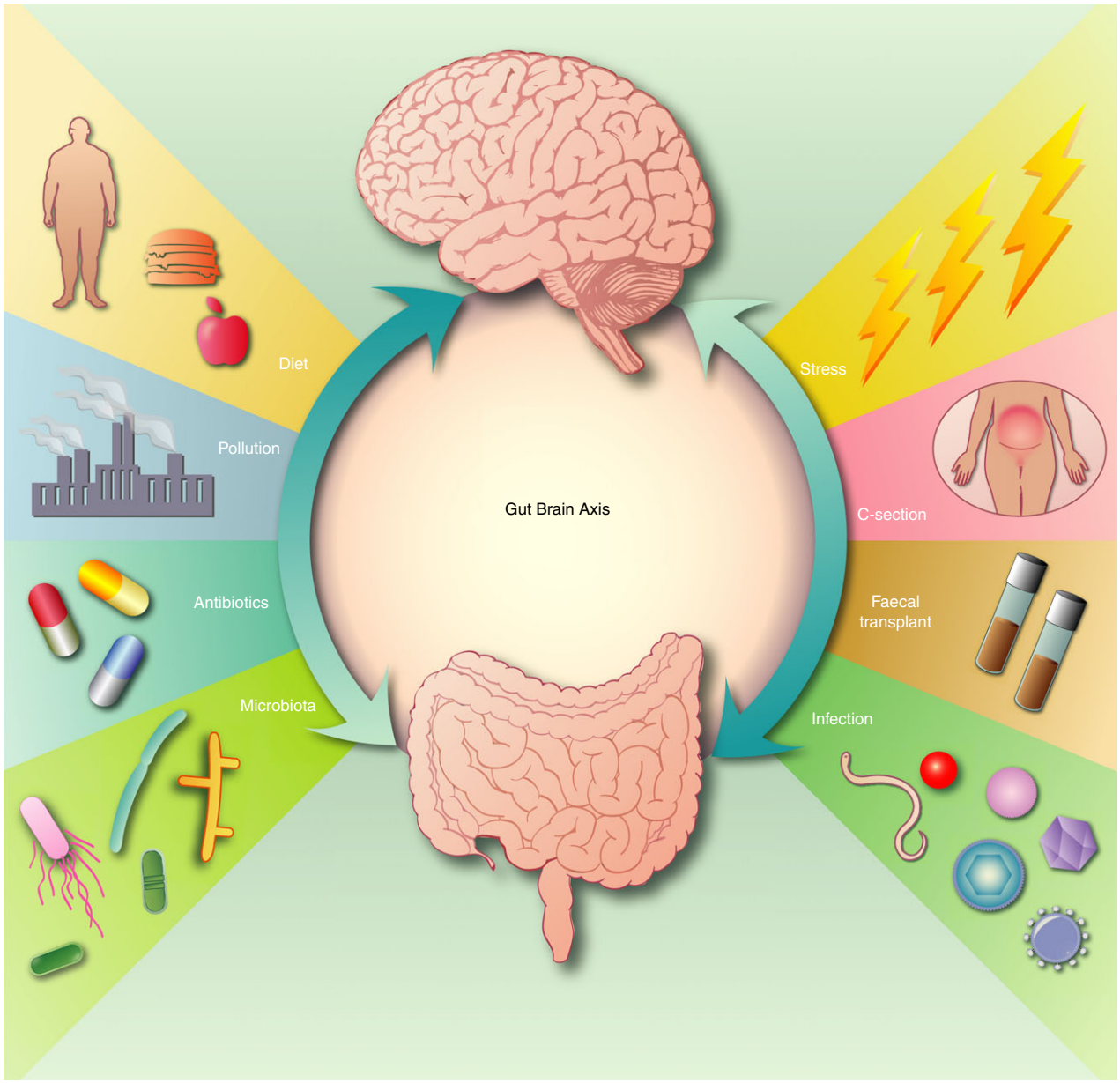

Figure 3. Proposed factors that influence the gut–brain axis in neuroinflammmatory disorders. Cross-talk (arrows) between the gut and brain indicates that lifestyle and the environment influence brain function that feeds back to the gut brain axis. Altered gut microbiota composition as a result of lifestyle, for example, poor diet, stress, infection and other environmental factors, enhances the risk of neuroinflammatory disorders. During development maternal inflammation and caesarean section may influence brain development and microbiome of the fetus. Therapeutic approaches using faecal transplants, controlled and restricted diet and probiotics may help establish a healthy microbiome and therefore improve brain health.

in other neurodegenerative diseases, this may be an important factor that drives progressive neuropathology with ageing. Ageing also affects one of the most important regenerative processes in the brain, *viz*: remyelination. The efficiency of this process progressively declines during ageing as a result of reduced signalling from macrophages to regulate differentiation of oligodendrocyte precursor cells.[108]

Monitoring neuroinflammation

Although biomarkers of neuroinflammation are considered essential for monitoring disease diagnosis, progression and response to therapy, there is a lack of accurate and reliable biomarkers for many neurological diseases.[109] Many biomarkers present in blood or CSF are a consequence of the CNS pathology, for example, cytokines and

Table 2. Environmental and lifestyle risk factors in neuroinflammmatory diseases

Risk factor	Potential mechanisms	Disease	References
Viral infections	↑pro-inflammatory cytokines, chemokines, ↑macrophages, ↑NK cells	↑ALS, ↑MS, ↑stroke, ↑autism[1], ↑schizophrenia1, ↑bipolar disorder[1]	91, 93–96, 98, 99
Bacterial infections	↑neutrophils, ↑complement, ↑pro-inflammatory cytokines	↑MS, ↑stroke, ↑schizophrenia[1], ↑bipolar disorder[1]	94, 95, 98, 99
Fungal infections	↑neutrophils, ↑pro-inflammatory cytokines, chemokines, ↑macrophages	↑MS, ↑ALS, ↑AD, ↑stroke	87, 92, 94, 95
Pollution	↑ROS, microglial activation, BBB changes, ↑pro-inflammatory cytokines, infiltrating monocytes, astrogliosis	↑stroke, ↑AD, ↑PD, ↑MS, ↑ALS, ↑autism[1]	90, 91, 96
Metals exposure	Neurotoxicity and metal aggregates, ↑ROS	↑ALS, ↑PD, ↑autism[1]	91, 92, 96
Pesticides	Neurotoxicity, ↑ROS, BBB changes, UPS inhibition, defective autophagy, ER stress, mitochondrial dysfunction	↑ALS, ↑PD, ↑AD	91, 92
Moderate alcohol consumption	↑pro-inflammatory cytokines, ↑ROS, ↑chemokines, astrogliosis	↓ALS, ↓AD, ↓PD, ↓MS, ↑stroke, ↑depression, ↑bipolar disorder	91–93, 95, 97, 99
Smoking	↑ROS, neurotoxicity, ↑pro-inflammatory cytokines	↑ALS, ↓PD, ↑AD, ↑MS, ↑stroke, ↑autism[1] (debated), ↑depression, ↑bipolar disorder[1]	88, 90, 91, 93–95, 97
Regular exercise	↑monocytes, ↑neutrophils, ↑NK cells	↑ALS, ↓AD, ↓PD, ↓depression	91, 92, 97
Obesity	↑macrophages, ↑pro-inflammatory cytokines, ER stress	↑ALS, ↑PD, ↑AD, ↑MS, ↑stroke, ↑depression	91, 92, 93, 95, 97
Head injury	↑neutrophils, ↑complement, ↑pro-inflammatory cytokines and chemokines, T-cell migration	↑ALS, ↑PD, ↑AD, ↑MS, ↑bipolar disorder	91–93, 99

[1]Prenatal exposure.

chemokines,[109,110] loss of BBB integrity[105] or indicators of neuronal damage, such as the increased levels of neurofilament[111] or decreased *N*-acetyl-aspartate levels on MRS.[109] One such pathological marker, extracellular vesicles (EVs), are released by neurons, oligodendrocytes, astrocytes, microglia and epithelial cells, as well as by immune cells that enter the brain during inflammation.[112] In neurodegeneration, EVs are widely considered to act as vehicles for the spread of aggregated pathogenic proteins. The composition of EVs closely reflects the cell from which they are derived. Upon entering the CSF or blood they should therefore be considered as potential biomarkers of disease progression.

While blood and CSF are commonly used to monitor biomarkers of neuroinflammation, *in vivo* imaging of the CNS during disease has become a more widely accepted approach due to its non- or minimally invasive nature. Such techniques include magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT) and optical imaging.[113] In this way, neuroinflammation can be studied by: (i) monitoring activation of resident CNS immune cells, for example, microglia activation; (ii) BBB permeability, for example, upregulation of adhesion molecules; (iii) CNS infiltration of immune cells; and (iv) pathology as a result of neuroinflammation, for example, demyelination and cell death (Table 3). For example, imaging of resident immune cells is frequently performed using PET to examine the translocator protein 18 kDa (TSPO) as an indicator of neuroinflammation in stroke,[119] AD,[120] MS[121] and epilepsy.[122]

In addition, BBB permeability, regarded as the hallmark of neuroinflammation, is imaged by leakage of gadolinium using MRI, or by nuclear imaging of P-glycoprotein and vascular cell adhesion molecule (VCAM-1), which are differentially expressed in MS,[123] stroke,[124] AD and vascular dementia.[125]

Indicators of leucocyte function include markers of oxidative stress, such as pro-inflammatory and oxidative enzymes secreted by activated monocytes and neutrophils. One such product is myeloperoxidase (MPO) that can be detected by gadolinium (Gd) (MPO-Gd) to track the oxidative activity of MPO non-invasively. Thus, MPO has been used as a potential biomarker of neuroinflammation in experimental models of MS, namely experimental autoimmune encephalomyelitis[126] and experimental stroke.[127]

Cell-labelling approaches include radiolabelled antibodies and radiolabelled cytokines, which are imaged using SPECT, PET or optical imaging. Radiolabelling of

Table 3. Biomarkers and imaging of neuroinflammatory diseases

Target type	Target	Marker	Methods	References
Resident CNS cells	Translocator protein	Innate immune activation	PET, SPECT	109
	Monoamine oxidase-b	Reactive astrocytes	PET	109
	Cyclooxygenase 1	Activated microglia and astrocytes	PET	109
	Myeloperoxidase	Inflammatory mediator found in leucocytes	MRI, PET	114
	Adenosine receptors	Cell injury	PET	115
	a4b2 nicotinic acetylcholine receptors	Activated microglia and astrocytes	PET	109
	Myo-inositol	Astrocyte hypertrophy	MRS	109
	N-acetyl-aspartate	Neuronal integrity	MRS	109
	Iron accumulation	Free radical formation, mitochondrial or neuronal dysfunction	MRI	116
	Myelin	Demyelination and loss of myelin integrity in white matter disorders	PET	109
BBB integrity	Vascular cell adhesion molecule 1	Activation BBB	Molecular imaging	109
	P-glycoprotein	Alterations of expression in relation to BBB activity	PET, optical imaging	109
Immune markers	Cytokines	Pro- or anti-inflammatory signals	CSF	110
	Chemokines	Pro- or anti-inflammatory signals	CSF	110
	Superparamagnetic particles of iron oxide (SPIO)	SPIO-labelled phagocytic cells	MRI	117
Antibodies	Oligoclonal bands	IgG of unknown specificity	CSF	111
	Anti-aquaporin 4 antibodies	Antibodies to aquaporin 4 (water channel protein)	Blood	111
	Anti-NF antibodies	Neuronal damage	Blood	111
Free proteins	Neurofilaments	Neuronal damage	CSF	111
	MicroRNAs	Circulating microRNAs involved in inflammation	Blood	111
	β-amyloid	Proteins involved in disease pathology	Blood	118
	Tau	Proteins involved in disease pathology	Blood	112
	Annexin V	Apoptosis	PET, SPECT, blood	109
	Exosomes	A potential mechanism by which pathology is spread and/or toxic proteins are transported	CSF/blood	112

Figure 4. Mechanisms of damage and therapeutic control of inflammation in neurodegenerative diseases. (1) In the central nervous system (CNS), damage to neurons or genetic mutations leads to accumulation of misfolded and aggregated proteins characteristic of many neurodegenerative diseases. Such damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) activate microglia and astrocytes to release pro-inflammatory factors. Likewise, stressed neurons and glia release heat-shock proteins (HSPs) in an effort to counter the formation of aggregated proteins. Some HSPs, for example, HSPB5, induce regulatory microglia and astrocyte phenotypes. Neuronal specific antibodies (2) activate the complement system or induce Fc receptor (FcR)-mediated damage. (3) Natural killer (NK) and T-cells damage neurons via MHC class-I, $CD8^+$ T-cells or non-classical MHC molecules. (4) Excessive production of glutamate together with reduced glutamate uptake by astrocytes leads to excitotoxic damage of neurons. (5) Macrophage/microglia activation triggers reactive oxygen (ROS) and nitrogen (NOS) species, MMPs, chemokines and cytokines known to damage axons and neurons. (6) B-cells secrete pathogenic antibodies and toxic factors that damage axons and oligodendrocytes. Therapeutic approaches to control neuroinflammation include (A) anti-CD20 antibodies to deplete B-cells that play multiple roles in immune-mediated neurodegeneration (see text for details). (B) IVIG and plasmapheresis block pathogenic antibodies, including those triggered by tumours as in paraneoplastic disorders. (C) Complement inhibitors control activity of complement, while (D) antioxidants and (E) calorie restriction reduce ROS and NO levels that contribute to neurodegeneration. (F) In multiple sclerosis (MS), inhibition of T- and B-cells entry across the blood–brain barrier (BBB) into the CNS, for example, (G) Natalizumab (Tysabri®), or immune therapies that deplete T- and B-cells [Alemtuzumab (Lemtrada®), or alter their function Glatiramer acetate (Copaxone®)] in the periphery, or (H) block immune cell trafficking from the lymph nodes (FTY720, S1PR-agonists) controls neuroinflammation in the CNS.

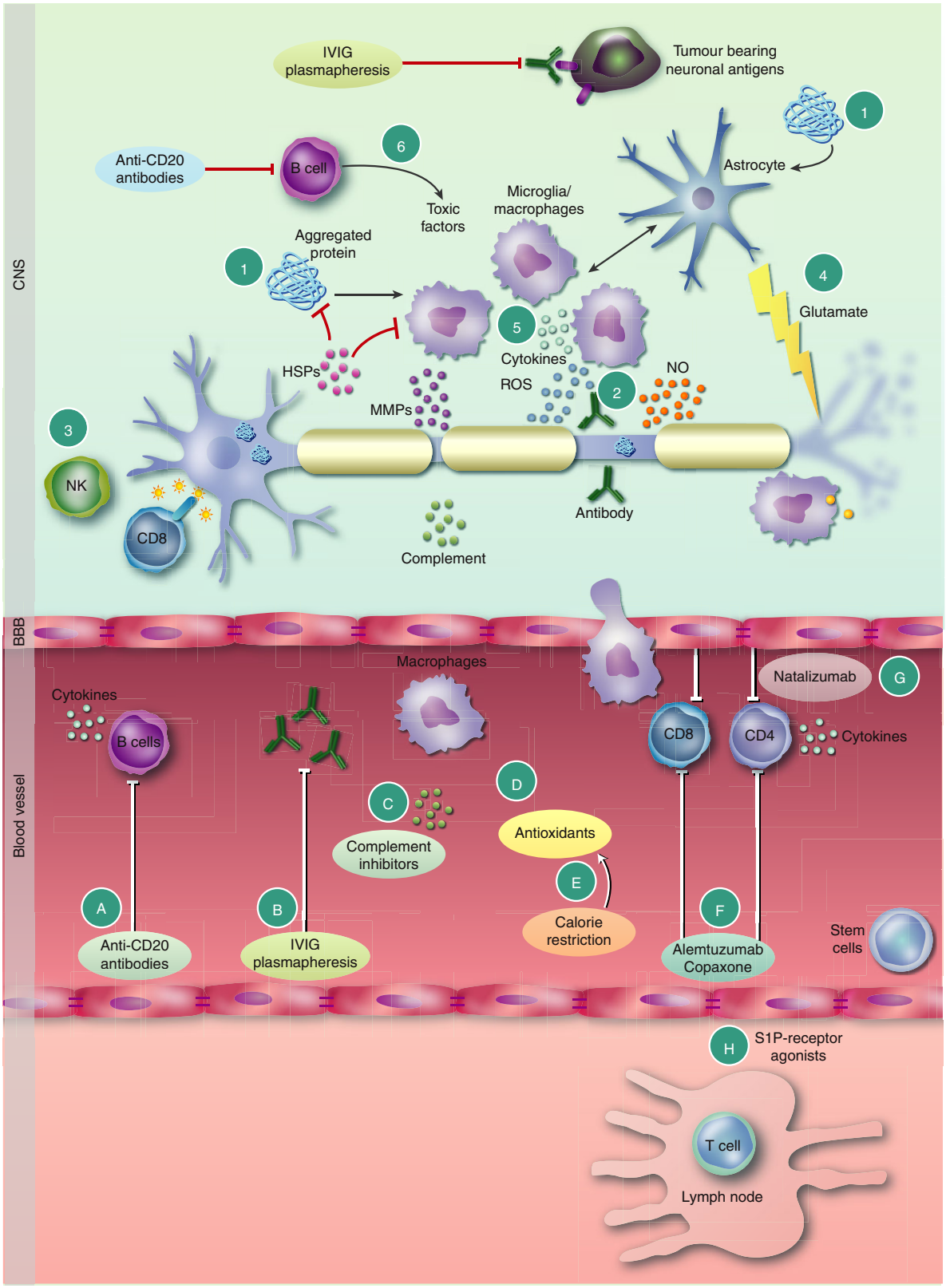

Table 4. Immune therapies in neuroinflammatory disorders

Therapeutic intervention	Proposed mode of action	Disease	References
Antibodies to abnormal protein aggregations e.g. a-synuclein, PrP	Clearance of aggregates	AD, prion diseases, HD, ALS, stroke, PND	132–135
Plasmapheresis (+tumour removal)	Removal of pathogenic antibody	Paraneoplastic disorders	136
Stem cell therapy	Creating non-pathogenic and reparative cell populations	MS, SMA, ALS, TBI, AD, PD, prion diseases, stroke, HD	137–144
Antibiotics e.g. minocycline	Inhibition of inflammation and anti-apoptotic activity	AD, ischaemia, PD, HD, MS	145,146
Cannabinoids	Attenuates excitotoxic glutamatergic neurotransmission, modulation of microglia and astrocytes	AD, PD, HD, ALS, epilepsy, MS, autism	133, 147–149
Non-steroidal anti-inflammatory	Inhibition of COX-1 and -2	AD	132
Diet and calorie restriction	Antioxidant functions, inhibits COX-2 and iNOS, reduction in free radicals and oxidative stress	Epilepsy, ALS, AD, PD	150–153
Anti-lymphocyte therapy	B-cell depletion (CD20) Plasma cells depletion (CD19) Blocking T-cell responses Modulating T-cell phenotypes	MS, stroke, depression	135, 137, 154
Innate immunity based therapy	Macrophage apoptosis and macrophage suppression. inhibition NLRP inflammasome inhibiting/modulating microglia phenotypes.	MS, depression, ischaemia, TBI	137, 141, 154
Targeting ionotropic and metabotropic receptors	Agonist/antagonist antibodies or ligands e.g. NMDA, glutamate receptor antagonist	AD, PD, HD, MS, SMA, ALS, prion disease, epilepsy, bipolar disorder, TBI, depression, schizophrenia	132–134, 137, 138, 141, 154–158
Antioxidants	Reducing ROS, upregulating antioxidant genes. Targeting Nrf2 pathway (e.g. BG12). HSPs.	MS, HD, ALS, stroke, TBI, schizophrenia, depression Friedreich's ataxia	134, 135, 137, 141, 154, 158, 159
RAGE antagonists	Reduction of formation or activation of innate immune responses by blocking/inhibiting advanced glycation end-products (AGEs)	AD	160
Complement inhibition	Blocking complement mediated neuronal damage	Stroke, TBI, epilepsy	161–163
Potassium and sodium channel targets	Neuroprotection e.g. lamotrigine, fampridine acid-sensing ion channel 1 (ASIC1)	MS	137
Chemokine/cytokine modulation	Promoting regenerative microenvironment e.g. IL-4, CD28, amplification of Tregs. CXCR3	AD, TBI, epilepsy, depression, schizophrenia, bipolar disorder	132, 141, 154, 157, 158, 164

anti-CD3, anti-CD4, IL-1 and IL-2 have all been used to visualize T-lymphocytes in MS[128] and rheumatoid arthritis.[129] As well as ongoing neuroinflammation, several approaches image the resultant pathology. As an example, PET ligands have been used to visualize myelin damage in MS,[130,131] while many approaches are used to visualize cell death, for example, neuronal loss, such as annexin-V, caspases and ML-10.[113] Imaging of neuro-inflammatory biomarkers is an expanding topic with the potential to expedite diagnosis, and improve disease and therapeutic monitoring. Unfortunately, while many approaches are examined in preclinical models, fewer are available for studies in humans.[109]

Immune therapies

The accumulating evidence supporting the notion that inflammation plays a key role in neurodegenerative diseases of the CNS has stimulated an increasing number of immunotherapeutic strategies to modulate

neuroinflammatory diseases (Fig. 4; Table 4). Many of these approaches that have been examined in MS may also be effective in other neurodegenerative diseases, as shown with Gilenya (FTY720, S1P-R agonist) for experimental PD.[165] Some approaches, such as gene silencing,[166,167] target a specific aggregated protein, while immune-based therapies including plasmapheresis or IVIG are specific for antibody-mediated disorders. However, other approaches, including antioxidant compounds, ion channel blocks, and approaches promoting neuroprotection and regeneration, such as haematopoietic stem cell transplantation and modified stem cells, are now being exploited in neurodegenerative disorders such as cerebral adrenoleucodystrophy.[168] Other approaches for modulating aberrant innate and adaptive immune cells are also under investigation, including the use of exogenous HSPs. As an example, HSPB5 exerts neuroprotective effects in several models of neurodegeneration as well in MS.[169]

Conclusions

That the nervous and immune systems are inextricably interlinked is reinforced by recent studies revealing meningeal vessels that directly link the brain with the lymphatic system. In many neurodegenerative diseases the innate immune response in the CNS plays a key role in the onset and progression of disease, but is equally important for resolution of inflammation. During development microglia aid in synaptic pruning and neurophagy,[53] which is important for neuronal development. Even at this early stage, environmental factors including maternal infections or alcohol intake influence microglial responses in later life. Similarly, adaptive and innate immune cells that enter the CNS trigger damage but are crucial for immune regulation. As well as the well-recognized roles of microglia, astrocytes and neurons, oligodendrocytes also contribute to immune surveillance and regulation in the CNS.

Thus, despite beneficial roles of immune responses, such responses must remain under tight control to prevent CNS damage. During ageing and repeated activation, immune cells undergo senescence, implying that the CNS is not fully protected. The factors that drive chronic inflammation include misfolded and aggregated proteins, HSPs and other DAMPs that trigger local innate responses. Infectious agents also play a role, including those arising from the gut microbiome and toxic compounds in the environment. Gene silencing to prevent protein aggregation is effective in experimental settings, and it is encouraging that studies in humans are now underway. Thus, development of novel therapeutic approaches to target the pathogenic mechanisms leading to detrimental inflammation, as well as harnessing endogenous protective pathways, will be key to controlling neuroinflammatory diseases.

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Disclosures

The authors have no conflict of interests to disclose.

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